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THE HUMPHREY CENTER REPORT

A publication of the Hubert H. Humphrey Cancer Research Center of Boston University

Humphrey Awards

Honoring three leaders in the fight against cancer

The Great Hall of Boston's renowned Quincy Market, brightened by the rays of an early spring sun, was the scene as this year's Hubert H. Humphrey Cancer Research Center Awards were presented to three distinguished recipients.

A luncheon gathering of 250 watched as the awards were presented to:

- Former U.S. Sen. Edward W. Brooke, honored for his efforts to increase the level of federal support for cancer research;
- Harry Eagle, M.D., associate dean and director of cancer research at Albert Einstein College of Medicine in New York City, honored for his contributions to cell biology and the use of tissue cultures in biomedical research; and
- Armand Hammer, M.D., well-known industrialist and currently the chairman of the President's Cancer Panel, honored for his philanthropic support of cancer research.

Hammer was given his award by Boston University President John R. Silber, who noted that the industrialist's ventures in international trade made him "a 20th-century rival to Marco Polo."

"His philanthropic career resembles his business career," Silber went on. "It has been carefully planned, perfectly targeted and open to the taking of well-calculated risks."

Hammer first traveled to the Soviet Union in 1921 to help people victimized by the health problems resulting from the Russian Revolution, said Silber. While there, he came to Lenin's attention, and was asked by the Soviet ruler to help restore his country's trade relations with the West—an episode that marked the beginning of Hammer's involvement in international trade.

Hammer, during the course of brief acceptance remarks, made the surprise announcement that he was contributing $50,000 to the Humphrey Center's hybridoma laboratory. (See photo of the lab on page 8).

Richard H. Egdahl, M.D., director of Boston University Medical Center, presented the Humphrey award to Brooke. He compared the honoree's contributions to those of Humphrey, saying that "like Hubert Humphrey, Ed Brooke well understood how to use the legislative process to help those in need."

Egdahl singled out Brooke's efforts to boost federal support for cancer research during the senator's tenure as a member of the Senate Appropriations Committee. "He was a major factor in riveting public attention on

continued on page 3

Winners of the awards and others chat during Humphrey awards ceremony. Shown are, from left, Luci Baines Johnson, member of the awards committee; University President John R. Silber; former Senator Edward Brooke; Armand Hammer, M.D.; Hubert Humphrey's sister, Frances Howard; Harry Eagle, M.D., and John I. Sandson, M.D., dean of Boston University School of Medicine.

What is the nature of the link between diet and cancer? Humphrey Center scientists are helping to shed light on this critical, and controversial, subject. See story, page 4.

FROM THE DIRECTOR

Dear Friends,

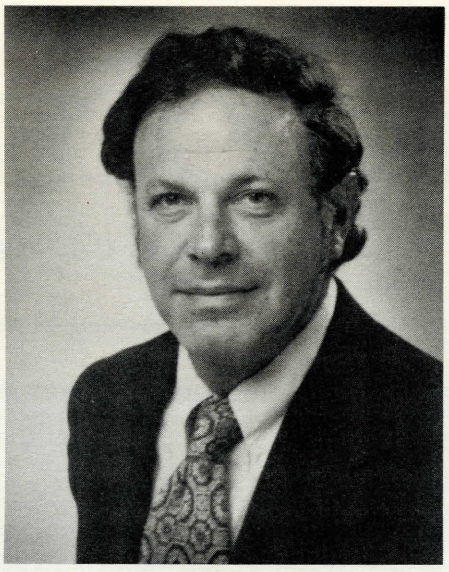
This new publication, *The Humphrey Center Report*, marks the initiation of a new effort on our part to keep you informed of Center activities. *The Report* will be published three times a year; any comments you may have are welcome.

In March, we held our third annual Hubert H. Humphrey Cancer Research Center awards ceremony, at which we honored three outstanding figures in the battle against cancer. The contributions of former Sen. Edward Brooke, Armand Hammer, M.D., and Harry Eagle, M.D., have been different in nature; they are alike, however, in what they say about the commitment and foresight of these three men.

The recent past also has seen steady progress on the Center's new home. It is to be located in totally renovated space on the seventh floor of what was formerly the Boston City Hospital Outpatient Building. When completed, it will help to provide a focus and a point of interchange for the more than 75 scientists who make up the Center's professional staff.

We have already received a site visit from the National Cancer Institute, which has been asked to provide part of the funding for the project. We are optimistic that NCI's decision will be favorable. Meanwhile, our thanks to those who have already supported the building campaign. We are particularly grateful for the substantial assistance pledged by the Louis B. Mayer Foundation, Clifford and Phyllis Seresky, and the Raytheon Company.

The basic mission of the Center is cancer research, of course, and the recent past has seen impressive progress on many fronts. One advance that attracted considerable public notice was the report by one of our staff members, Frederick Moolten, M.D., that he had developed a vaccine that successfully protected experimental animals against a cancer-causing agent.



In addition, two staff members, Michael Osband, M.D., and Ronald McCaffrey, M.D., reported in the *New England Journal of Medicine* that they had developed a treatment that corrects an imbalance in the immune system associated with the children's disease called Histiocytosis-X. Although this is a very rare condition, the treatment is expected to be applicable to several other, more common ailments.

The Center's research activities, as many of you know, are organized around working groups. These groups have been set up in order to promote close and frequent interchanges among Center staff members involved in similar areas.

So far, six of the working groups are in place. They are the groups focusing on cancer as it relates to: nutrition; cell biology; new strategies in cancer therapy; hormones; the underlying causes of the disease; and advances in treatment methods (the last is designed especially for staff members involved in clinical work). The seventh group, concerning cancer and the immune system, will be set up over the course of the coming months.

As part of our research role, we seek to extend knowledge about recent advances to the broader research community. One part of this effort is the annual Sidney R. Cooperband Symposium, named for the Center's first director. The third in the symposium series was held in November, with Robert K. Oldham, M.D., director of the NCI's Frederick Cancer Research Center in Frederick, Md., as lead presenter, and drew a gratifying level of participation. Fortunately for all of us, Oldham remained at BUSM for several days in his role as the first Charles E. Culpeper Visiting Professor in Immunology.

The Center also supports a variety of lecture series. A current one, sponsored jointly with the Division of Psychiatry, is on the fascinating subject of the role played by mental processes in promoting or suppressing tumors.

The Center also tries to communicate knowledge to physicians and nurses involved in treating cancer. This is done through our Regional Oncology Program, under the direction of Peter Deckers, M.D. Program seminars are held at several hospitals throughout southeastern Massachusetts, and continue to draw an enthusiastic response from practitioners.

The period ahead promises to be at least as eventful as the last several months have been. One major milestone will be our application for renewal of core funding from NCI, scheduled for the fall. Here again, we are optimistic. Whatever the future may hold, though, the Center is today a vibrant and active organization, with a range of research undertakings that is truly exciting to all of us.

Regards,

Paul H. Black

Paul H. Black, M.D.

Awards . . .

continued from page 1

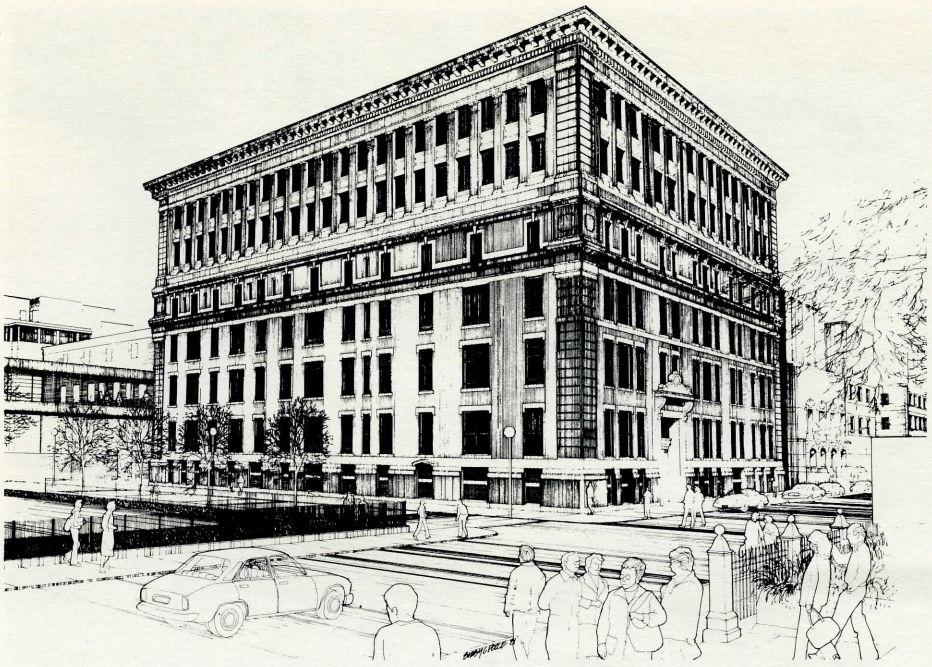
the importance of adequate funding for both clinical and basic research in cancer."

The third honoree, Eagle, was characterized by John I. Sandson, M.D., dean of Boston University School of Medicine, as a "statesman of science, one who understands how to make practical the findings of the research laboratory."

Eagle, he noted, was a member of the U.S. Public Health Service from 1936 to 1961, and during that period rose to become chief of the Laboratory of Cell Biology at the National Institute of Arthritis and Infectious Disease.

During the luncheon gathering, Paul H. Black, M.D., director of the Humphrey Center, provided an update on Center activities over the past year. Boston Mayor Kevin White and a representative of Gov. Edward King also spoke.

The awards program was established three years ago when the Center was renamed for the late Minnesota Senator and 38th Vice President of the United States. In addition to Muriel Humphrey Brown, previous awardees have been: Sidney Cooperband, M.D., the Center's first director (posthumous); David Baltimore, Ph.D., the American Cancer Society Professor of Microbiology at the Massachusetts Institute of Technology and winner of a Nobel prize for his research on the interaction between tumor viruses and the cell; Marvella Bayh, the late wife of U.S. Sen. Birch Bayh, honored for her efforts to educate the public about the importance of cancer prevention (posthumous); Mary W. Lasker, a philanthropist and the organizer, along with her husband, of the American Cancer Society's first public fundraising appeal; and George Thorn, M.D., formerly physician-in-chief at Peter Bent Brigham Hospital and a professor at the Harvard Medical School, who was cited for his research on the role of hormones and the adrenal gland in cancer development.



Center will occupy top floor of this building, shown here in artist's rendering.

Work proceeds on Center's new home

The Hubert H. Humphrey Cancer Research Center currently has a strong organizational identity but lacks a physical one: There is no place it can call home.

That circumstance is expected to change within about a year, though, when the Center's headquarters and some of its labs move into the former Boston City Hospital Outpatient Building, located across the street from the School of Medicine.

The seven-story structure, which has not been in use since the hospital's new Ambulatory Care Center opened in 1978, is being totally renovated. When the work is done—which is scheduled for mid-1983—the Humphrey Center will occupy the top floor, and other elements of the School of Medicine and University Hospital will occupy the remainder. The building will be called the Boston University School of Medicine Centers for Advancement in Health and Medicine.

The Humphrey Center's floor is being renovated and equipped at a cost of approximately $1.2 million. The Center has applied to the National Cancer Institute for roughly half the cost, and will raise the rest through a unified fundraising campaign with the other prospective occupants of the building.

The new facility will play an important role in focusing and coordinating the Center's wide-ranging research enterprises, said Isaac M. Taylor, M.D., associate director for administration. In addition, it will provide laboratory and office space for several of the Center's more than 75 professional staff members.

Several major donations already have been made to support development of the Center facility. They have come from:

- the Louis B. Mayer Foundation, which is supporting development of the tumor cell biology laboratory;
- Clifford and Phyllis Seresky of Canton, Mass., who are supporting development of the immunology lab; Mr. Seresky is the brother of Selma Cooperband, widow of the first director of the Cancer Center; and
- the Raytheon Company, which is making its first corporate donation to a school of medicine in providing support for the Center's new facility.

Cancer and Diet:

Probing the nature of the connection

Few subjects have been surrounded by more confusion and controversy than the link between diet and cancer.

That there is a link is without doubt. Studies of stomach cancer, for example, have shown that when people move from Japan, which has a very low stomach cancer rate, to the United States, which has a higher rate, their chances of contracting the disease rise until they approximate those of U.S. natives.

Studies of different populations in the U.S. also argue for a diet-cancer connection. The rate of colon cancer among Mormons, for example, is much lower than the U.S. average. Scientists believe the main reason is the Mormon diet, which includes no stimulants or alcohol and is high in vegetables and fruit.

Unfortunately, the nature of the diet-cancer relationship is still poorly understood. Much of the information about it has come from studies like those of the experience of Japanese immigrants to America. Such studies can offer clues to the kinds of food that need attention. The Japanese diet, for example, is high in fish. But the studies do not pinpoint how specific foods and nutrients affect the development of cancer.

"In light of the increasing support within the scientific community for the concept that diet and nutrition might play a major role in the initiation and progression of certain human cancers," said Paul H. Black, M.D., Humphrey Center director, "there is a need for scientists to clarify the nature of the interaction. Several of the investigators at the Humphrey Cancer Research Center are involved in studies that will accomplish exactly that."

One group of investigators at the Center, for example, is focusing on the role of fats in promoting cancer. Included in their research is an examination of one of the most medically renowned of all components of the diet—cholesterol.

Other researchers are looking at the role of vitamins in controlling tumor growth. One series of studies focuses on vitamin E, the nutrient that is most commonly found in vegetable oils. Another series involves vitamin A, the nutrient that is found in such foods as carrots, eggs, fish and leafy vegetables, and is critical to sustaining good eyesight.

The puzzling case of cancer and cholesterol

"There certainly is a correlation between a high-fat diet and cancer, just as there is a correlation with cardiovascular disease," said Joseph J. Vitale, M.D., Sc.D., director of the Boston University School of Medicine nutrition education program and a professor of pathology.

On the other hand, the strategy advised for cutting the risk of heart disease—substituting polyunsaturated fats, like those in corn oil, for the saturated fats found in milk and butter—may not protect against cancer.

The reason, said Vitale, is that polyunsaturated fats, while low in cholesterol, may have the paradoxical effect of increasing cholesterol levels in the intestinal tract.

Cholesterol, he explained, is an essential component of the human makeup, forming a part of every cell in the body. In addition, said Vitale, the body has the ability to regulate its cholesterol levels. Thus, in general, he said, "if you eat more cholesterol, your body makes less, and vice versa."

Substituting polyunsaturated fats for saturated fats does in fact cut blood levels of cholesterol. Yet the unsaturated fats appear to accomplish this by affecting the regulatory mechanism in such a way that the "extra" cholesterol and other cholesterol-like substances—the amount removed from the blood—enters the intestinal tract.

Is this added cholesterol in the gut something to worry about? Yes it is, said Selwyn A. Broitman, Ph.D., a BUSM professor of microbiology and nutritional sciences.

"If we feed diets high in cholesterol to experimental animals, and then inject a substance known to cause tumors into the animals, the number of large-bowel tumors will go up," Broitman explained. This simply indicates that a high-fat diet increases the risk of cancer—a finding also supported by studies of cancer patterns among humans.

"On the other hand," said the microbiologist, "if we reduce serum cholesterol levels by feeding the animals polyunsaturated fats, that also increases the number of large-bowel tumors." This strongly suggests that the polyunsaturated fats are raising cholesterol levels in the intestinal system.

There is a variety of theories about how cholesterol promotes tumors, most of them focusing on its impact on the body's immune system.

As Vitale noted, there is strong evidence that cholesterol tends to reduce immunity. This may occur, he said, through its effect on a key component of the immune system called the macrophage—a cell that has the capacity to absorb or otherwise protect against such dangerous intruders as toxic chemicals or infectious bacteria, and to kill tumor cells.

"To function properly," said Vitale, "a macrophage has to have a certain level of fluidity. If you make it too fluid—too relaxed—it won't work. And if you make it too rigid, it won't work."

Recent research, he added, shows that cholesterol plays a key role in determining the fluidity of cells. Thus, what cholesterol may be doing is essentially disarming one of the body's leading defenders against cancer.

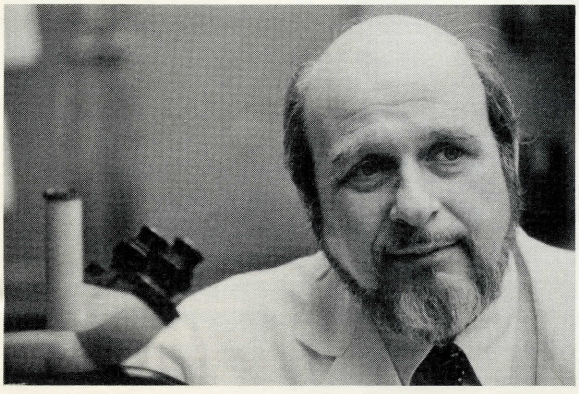
Currently, Broitman, Vitale and their colleagues are pursuing answers to a range of still-pending questions on the cancer-cholesterol link, and on the more general issue of the role of dietary fats in promoting cancer and affecting the immune system.

One of their main projects is to keep detailed records of the foods consumed by a group of cancer patients. This project—which also involves analysis of the patients' blood and other measures that will provide information about the group's dietary patterns—is intended to clarify what, up to now, has been a disputed subject.

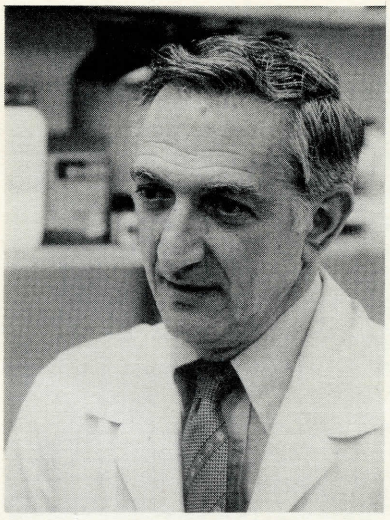
Trying to tell from personal recollections how much fat an individual consumes is very difficult, Broitman said. Many foods, like meat, have widely varying amounts of fat, and cooking can compound the divergence. "We're trying to find a difference of 5 to 10 percent in fat consumption from patient to patient, and you just can't do that by relying on recollections."

Thus, this study could help to provide one of the first accurate portrayals of how fat intake relates to the growth or suppression of tumors.

Research of this kind will ultimately provide doctors with clear guidance about how fat intake should be adjusted in cancer patients. Broitman expects that within about five years, enough will be known so that regulating the amounts of fat patients eat will start becoming a normal part of cancer therapy.



Selwyn Broitman, Ph.D.



Joseph Vitale, M.D., Sc.D.

Signs of an anti-tumor role for vitamins

Vitamins A and E are widely recognized as important nutrients. Every cereal box lists them, along with other nutrients, as essential parts of each person's diet.

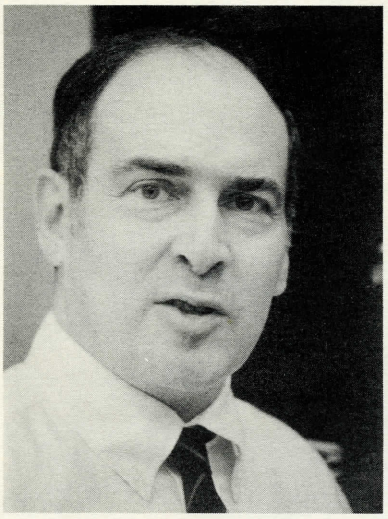
Cereal boxes, however, do not explain why these substances are important, nor how they are used by the body. Research now under way at the Humphrey Center is helping to illuminate such questions as they relate to preventing and treating cancer.

One of the investigators involved in vitamin E studies is Laurence Corwin, Ph.D., a professor of microbiology and nutritional sciences at BUSM.

Animal experiments carried out by Corwin and his colleagues have shown a clear connection between vitamin E and cancer. "If you give a high dose of vitamin E to laboratory animals," he explained, "and then subject them to a carcinogen, you find the nutrient will decrease the incidence of tumors to a highly significant degree."

An intriguing outcome, but what accounts for it?

According to Corwin, other experiments have convincingly shown that vitamin E stimulates the immune system. This is important because of the nature of cancer cells. "Most human



Laurence Corwin, Ph.D.

tumors are very poor at generating an immune response," he said, "and this is why they are so damaging—they are able to grow without getting the body's natural defenses activated."

In seeking answers to the question of how vitamin E energizes the immune system, Corwin and his colleagues have been focusing on chemical changes that occur on the cell surface. These changes, which are given the generic title of antigens, trigger the immune system. The system, in turn, can then go to work to destroy or remove the cancerous cells.

Corwin and his fellow investigators have found that the antigens present in the tumor cells they are studying do not stimulate the immune system very well.

Why not? One promising theory, said the microbiologist, is that something is chemically masking the antigens and thus preventing them from triggering an immune response. That something, they believe, is a substance called sialic acid.

"It has been found that many tumor cells have an increased sialic acid content compared with other kinds of cells," said Corwin. "We did some experiments, and we found that tumor cells with vitamin E had less sialic acid than those without it."

The next step in the research will be to try to complete the loop by demonstrating that antigens are more likely to stimulate the immune system when cells carrying them have been treated with vitamin E. In addition, there will be an effort made to identify the antigens involved.

The research on vitamin E opens some exciting possibilities in terms of treating and possibly preventing cancer. Unlike other nutrients, vitamin E is non-toxic: Large doses can be ingested without making people sick. In fact, Corwin already is involved in a study in which vitamin E is being given to a group of people to see how it affects their immune systems.

Aside from uses in therapy, another long-range possibility is the development of a method for immunizing people against some forms of cancer, just as people today are immunized against diseases like measles and polio. "It's clearly not feasible to immunize against cancer by using a tumor cell," Corwin said. "But if we know what antigen protects against a particular form of cancer, maybe that antigen can be used to provide immunity."

Besides vitamin E, another essential nutrient, of course, is vitamin A. As with vitamin E, there is strong evidence that vitamin A may help protect against cancer.

Edward Schroder, Ph.D., an assistant professor of microbiology at BUSM and a Humphrey Center member, is one of the investigators involved in vitamin A research. "Several studies have shown that if experimental animals are deprived of vitamin A, they are at higher risk of developing certain types of tumors," Schroder explained.

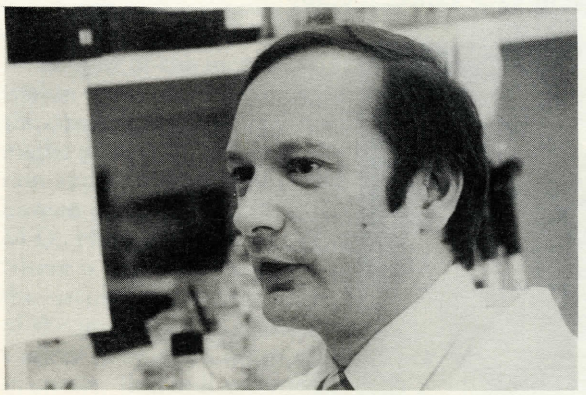
Other experiments, he added, have demonstrated the corollary: That vitamin A is helpful in reducing the risk of such forms of the disease as breast, colon and bladder cancer.

Not at all clear, though, are the mechanisms by which vitamin A does this. Schroder and his colleagues are trying to find out what these mechanisms are.

They have been working with a derivative of vitamin A called retinoic acid, and focusing specifically on the question of how it affects cell growth. Through this work they have discovered that when it is applied to tumor cells from rodents, retinoic acid will slow the rate at which the cells divide. Their research also suggests that the slow-down is linked to retinoic acid's effect on levels of a substance called adenosine-triphosphate, or ATP, which is known to regulate the rate at which cells divide.

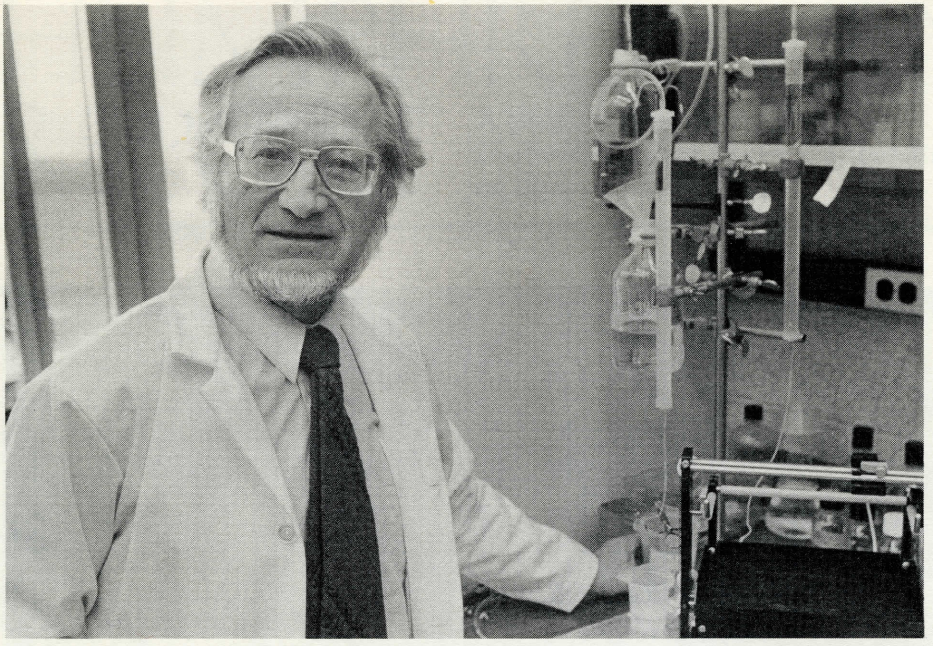
The next step, said the investigator, will be to try to tie their findings to human cancer. "We are going to look at cells derived from human tumors, to see whether their ATP levels also are affected by retinoic acid, and whether changes in ATP are correlated with changes in cell growth, and in the expression of other properties of tumor cells."

And what about potential applications in treating cancer? There is a need for caution in putting vitamin A to work in treating patients, Schroder said, because, unlike vitamin E, large doses of vitamin A can have toxic effects. Nevertheless, the notion of a substance that can slow the rate at which cells replicate—the basic process that drives tumor growth—raises the prospect of making significant inroads against many forms of cancer.



Edward Schroder, Ph.D.

RESEARCH PROFILE



Hugues J.-P. Ryser, M.D.

The curiosity that fuels a quest for basic answers about cancer

For most his career, Hugues J.-P. Ryser, M.D., has been engaged in one form or another of basic research.

It is research that may, in time, help to promote major advances in cancer treatment. For example, his work on the question of how large molecules penetrate cells, and how they are "digested" once inside, is directly applicable to cancer drugs. Thus, it could lead to methods for speeding the entry of drugs into tumor cells, and improving their effectiveness once they are in there.

Such applications, however — as Ryser himself emphasizes — lie far down the road. There is a need for a lot more experimentation, and many obstacles remain to be overcome.

Yet that has not discouraged Ryser, a professor of pathology, biochemistry, pharmacology and public health, and a member of the Cancer Center. He is deeply committed to involvement in basic research, and obviously enjoys it.

The commitment, though, is not one that dates back to his student days. For like many biomedical investigators, Ryser started out in medicine assuming that he would be a physician in practice.

Thus, although he took a research position after graduating from medical school in his native Switzerland, he did not see that as the start of a career in research.

"I had gone to medical school to be a doctor, I wanted to be a doctor and I felt I would be very good at being a doctor," he says. Thus, after about a year in research, he said to himself, "enough of this nonsense. I am now going to do my internship and my residency".

He signed on at one of the leading hospitals in Switzerland. Yet even there, more or less by accident, he wound up devoting some of his time to research.

Eventually concluding that research was perhaps where his future lay after all, he began looking for a position in the United States.

"In the late '50s," he says, "the United States was by all odds the center of biomedical research in the world. Boston was a particularly active area, as it is today."

The young physician was appointed as a research and clinical fellow at the Massachusetts General Hospital. His main focus, initially, was clinical research. But then he began looking at how large molecules penetrate cells.

"I found out that I was much happier doing research at the cellular level than I was at the level of a very complex disease," he recalls. "This probably has something to do with the fact that my mind functions in a mostly analytical way. I'm very comfortable analyzing basic phenomena."

Fascinated by the subject of macromolecules and cells, Ryser pursued it even though, at that time, there was dispute within the scientific community about whether large molecules could even get into cells.

As the result of his tenacity, Ryser in 1968 received the kind of recognition that comes rarely to a young scientist. He was asked to write a major article on macromolecular uptake by cells for the journal *Science*.

"There was a tremendous response to the article," he says. "Most of it was favorable, but there was a lot of condescending criticism, too."

Although Ryser will disclaim major responsibility, the field of macromolecular transport took off in the period following the article's appearance and it remains a major field of interest today.

The investigator's own work, of course, has gone far beyond simply examining how large molecules enter cells. One of the main areas that he and his associates, Wei-Chiang Shen, M.D., and Richard Mandel, M.D., are pursuing involves conjugates—that is, two molecules that have been chemically linked.

"We found many years ago that the uptake of macromolecules by cells increases markedly if they are linked to certain other types of macromolecules—those with a strong positive charge," he says. The increase in the rate of penetration can be enormous—as much as 1,000 times what it is for unlinked molecules.

The potential usefulness of this finding lies in the fact that cancer

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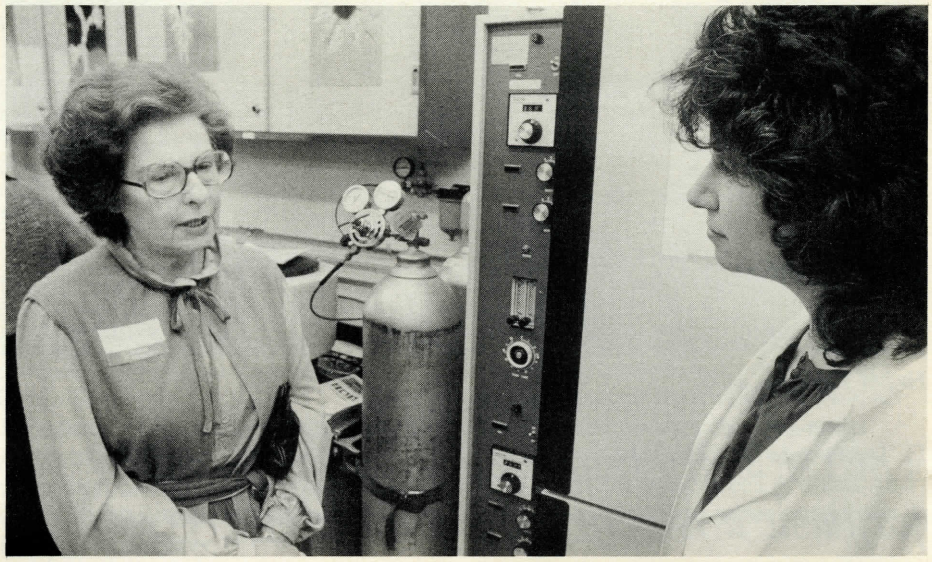
drugs are not readily able to penetrate cells. More recent work, says Ryser, has shown that the amount of an anti-cancer drug called methotrexate that gets into tumor cells growing in test-tubes can be increased tremendously through the linkage system.

While Ryser and his associates are trying to increase understanding of the role of macromolecules in penetrating cells, the investigator is also proceeding along many other scientific pathways. Some of these other projects may turn out to have early practical applications. His study of how cadmium and nitrosamines interact to increase the risk of cancer, for example, will help regulatory agencies decide what levels of cancer-causing substances to permit in the environment.

For the most part, though, his work is basic research upon which other investigators will be able to build—a fact that in no way diminishes Ryser's conviction about its importance.

"Nothing would happen, in medicine or any other area of science, if people did not first develop a certain intellectual curiosity about a phenomenon," he says. "There are some people—and I happen to be one of them—who are curious about what is going on in nature. And basic research is really just a systematic way of trying to find out."



Ann Marshak-Rothstein, Ph.D., (right) an assistant professor of microbiology and director of the hybridoma lab, chats with Aid for Cancer Research member Louise Shivek during dedication.

New hybridoma lab is dedicated

The Humphrey Center's new hybridoma lab, made possible through a donation by the Boston-area charitable group Aid for Cancer Research, was dedicated in March.

The facility is being used in one of the most exciting areas of cancer research—the creation of hybridomas. These are combinations of a cancerous cell with a non-cancerous cell. They are valuable because they allow creation of tumor-fighting substances called antibodies.

Traditionally, antibodies for use in either research or treatment have been produced by using experimental animals. This, however, is a slow and expensive process. With the use of hybridomas, antibodies can be produced much more rapidly, and in large quantities when necessary.

The reason for linking the two types of cells is that tumor cells are essentially immortal, whereas the nonmalignant cells—which generate the antibodies—would die too quickly to permit efficient production of antibodies if they weren't linked to a cancerous cell.

Aid for Cancer Research contributed $51,000 to equip the new lab. Well-known industrialist Armand Hammer, M.D., one of this year's Humphrey Center award winners, also has contributed $50,000 for the operation of the lab.

The Humphrey Center Report is published by the Hubert H. Humphrey Cancer Research Center of Boston University to keep its members and supporters abreast of recent Center activities and research advances. **The Humphrey Center Report** is produced by Boston University Medical Center's Office of Informational Services, Owen J. McNamara, director; Marjorie H. Dwyer, publications manager; Richard P. Anthony, editor. Designer: Nannette Gonzalez Kredlow, Boston University Design Office. Correspondence may be directed to the Hubert H. Humphrey Cancer Research Center, 80 East Concord St., Boston, MA 02118, or by calling (617) 247-6075. Paul H. Black, M.D., is director; Isaac M. Taylor, M.D., is associate director for administration.